Message

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Subject: RE: Chloroprene PBPK: in vitro data / parameters

Further below is a table of my findings with the in vitro modeling scripts, where discrepancies or concerns are highlighted. Some appear to be cases of the wrong value in the plotting script, but presumably the correct value in the MCMC analysis scripts. The impact on the plotted figures is mostly minimal, no consequence to the correction. I highlight the first instance of the kidney vial volume being different from that of the male lung/liver and female lung/liver, but otherwise it is mostly consistent. The notes below assume that difference in VVIAL for the Yang study is valid. These do not address the statistical model or how uncertainty in the RLOSS term should be addressed, that I went into in my previous email.

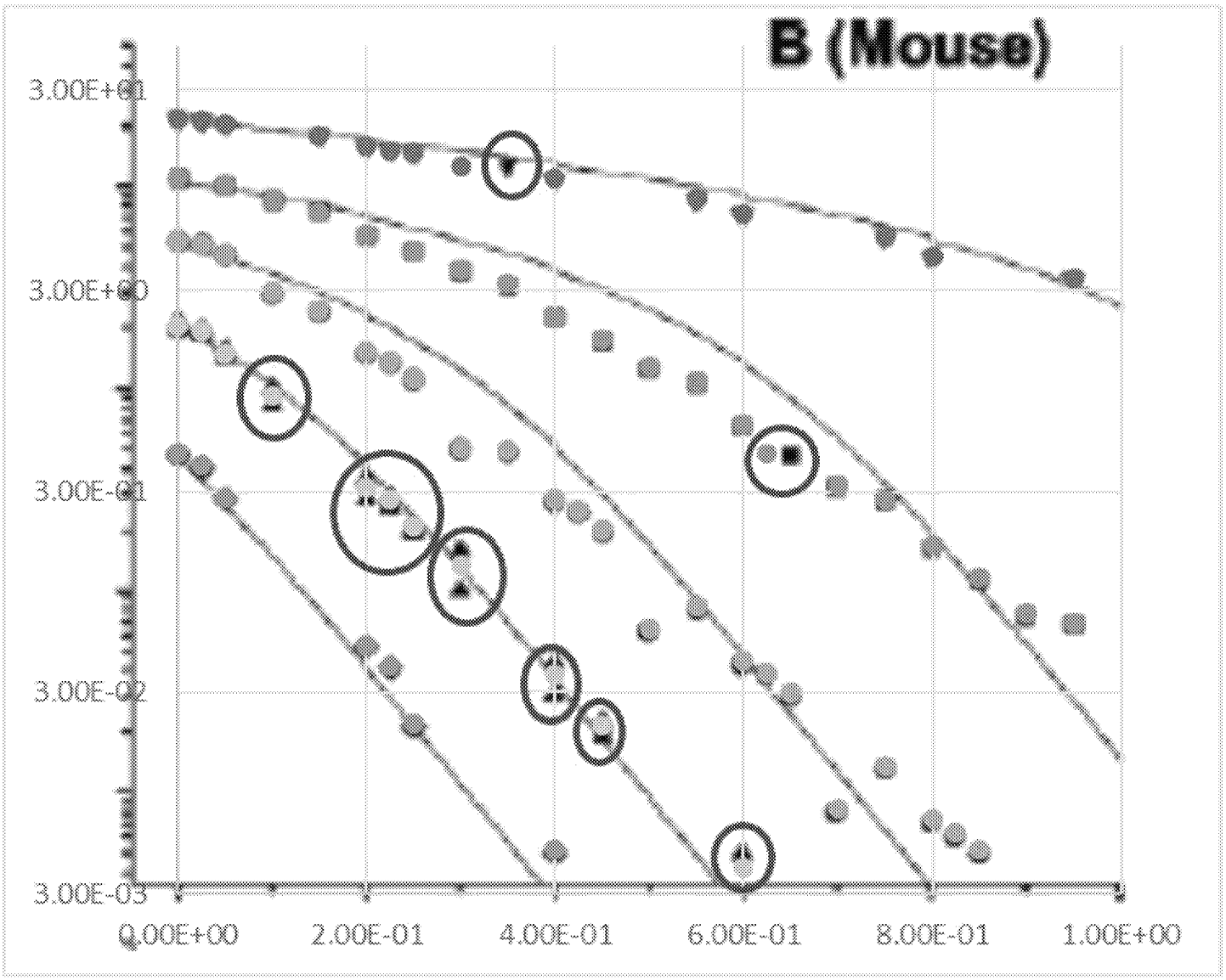
1) FMouse_KidneyMCMC1lvlvk.m appears to use the wrong VVIAL; though the difference likely will have little impact, it would be good to run again using the correct value
2) MMouseKidneyMCMC1lvl.m uses the wrong VVIAL and VINJ, where it is hard-coded into the function defined lower in the script. Since this rate is otherwise small, the impact on the estimated parameters will be relatively large, though it may not be significant to whole-body metabolism in the PBPK model. Still, the analysis should be run with the correct volumes.
3) FRatLiverMCMCrun.m: in the plotting script, VMED = 0.002 in the plotting script, but 0.001 in the MCMC file. I'm not sure of the impact, but one of the files should be corrected, MCMC run again if that's the error. This is the only place where VMED is different from 1 mL.
4) Female_rat_kidney.m vs. FRatKidneyMCMC1lvl.m: PROT = 1 in the plotting script, 2 in the MCMC script. I'm not sure which is correct, but the MCMC would need to be run again if that's in error.
5) VINJ = 0.004 in mixed human liver and lung analysis: mixed_human_liver.m had the value otherwise used for male mouse and rat liver and lung results (0.0003858); i.e., all other experiments reported in Himmelstein et al. (2004). The difference in value matters in estimating human lung metabolism. I have corrected the plotting script to use 0.004 (and also changed the model to simulate the effect as a continuous clearance = VINJ/TINJ), assuming that the sampling was indeed refined to this volume before conducting the human tissue experiments. An email from Matt Himmelstein was mentioned, but I looked back at all the emails I have from

him and could not find verification of this difference therein. Considering the impact, it would help if Ramboll could provide some record of this change.

The other thing that we'll need eventually are as much in the way of original data files in Excel spreadsheets as are available. Statistician reviewers may want to look at the raw data, not as embedded in acslX scripts. In particular, if data for individual incubation vials are available (vs. grouped into single measurement vs. time arrays), such as were provided for the control incubations, those are ideal. I understand that at the time of the original Himmelstein paper, they didn't create reports like they did for the Yang paper. So for those we may need to attempt (later) to reconstruct things, based on the timing of points. But the closer we can get to original data, the better.

Below is an overlay of the male mouse liver plot from Matt's paper with colored points from the acslX data array. Most of them line up adequately, but I have circled in red places with discrepancies. (For the 2nd form lowest data set, it looks like a number of the acslX values are roughly averages of distinct points above and below them.) The missing or displaced data will have some impact on estimates of parameter uncertainty, though from my review so far I think this may only occur in a couple of these sets where there are many points.

-Paul



File name	Metabolc parameters set	Disp.
female_mouse_liver.m	VMAX1 was set to 0.11 but listed as 0.108 in Table S-3. In "Posterior Parameters n IVIVE 6 25 2019.xlsx", after changing the number of sig figs shown, 0.108 is confirmed. Changing the value to 0.108 in the script did not significantly impact on the visual plot (on the semi-log scale used). VINJ=0.0002; VVIAL=0.01165; VMAX1=0.108; KM1=0.46; KF=0.0;	VMAX1 set to 0.108
FMouseLiverMCMC1lvl.m	VVIALF, VINJF, and other system parameters set at top of script match; numerical assignments on lines 105-110 also match.	
female_mouse_lung.m	VINJ=0.0002; VVIAL= 0.01165; VMAX1 =0.028; KM1=2.91; KF=0.0;	
FMouse_lung_mcmcrun.m	VVIALF, VINJF, and other system parameters set at top of script match; numerical assignments on lines 107-112 also match.	
female_mouse_kidney.m	VINJ=0.0002; VVIAL=0.01163; VMAX1=0.0; KM1=0.28; KF=0.00043;	
FMouse_KidneyMCMC1lvlvk.m	VVIALF, VINJF, and other system parameters set at top of script match; however, on line 91 it appears VVIAL for females is set to 0.01165, discrepant with value used for other kidney simulations. Impact? Other assignments on lines 92-96 match.	??
male_mouse_liver.m	VINJ=0.0003858; VVIAL=0.0119573; VMAX1=0.23; KM1=0.61; KF=0.0;	
MMouseLiverMCMC1lvl.m	VVIALM, VINJM, and other system parameters set at top of script match; numerical assignments on lines 102-107 also match.	
MMouse_liver_mcmcKG.m	VVIALM, VINJM, and other system parameters set at top of script match; numerical assignments on lines 99-104 also match. I have not checked every line vs. preceding script but it appears to be effective duplicate.	
male_mouse_lung.m	VINJ=0.0003858; VVIAL=0.0119573; VMAX1=0.13; KM1=1.72; KF=0.0;	
MMouse_lung_mcmcrun.m	VVIALM, VINJM, and other system parameters set at top of script match; numerical assignments on lines 97-102 also match.	
male_mouse_kidney.m	VINJ=0.0002; VVIAL=0.01163; VMAX1=0.010; KM1=0.58; KF=0.0;	
MMouseKidneyMCMC1lvl.m	VVIAL, VINJ, and other system parameters set at top of script match; numerical assignments on lines 97-102 also match. However, the values of VVIAL and VINJ hard-coded on line 98-99 are 0.0119573 and 0.0003858; i.e., values for male liver and lung experiments. The difference in VINJ in particular is enough to be significant to kidney Vmax and Km, though impact on PBPK likely to be small.	??
Female_rat_liver.m	VINJ=0.0002; VVIAL= 0.01165; VMED=0.002; VMAX1 =0.072; KM1=0.74; KF=0.0;	
FRatLiverMCMCrun.m	VVIALF, VINJF, and other system parameters set at top of script match; numerical assignments on lines 98-103 also match;	

	VMED=0.001 on line 12. Analysis should be re-run with correct VMED, or value corrected in plotting script.	
Female_rat_lung.m	VINJ=0.0002; VVIAL= 0.01165; VMAX1 =0.0; KF=0.00041;	
FRatLungMCMCrun.m	VVIALF, VINJF, and other system parameters set at top of script match; numerical assignments on lines 99-104 also match.	
Female_rat_kidney.m	VINJ=0.0002; VVIAL= 0.01163; VMAX1 =0.0036; KM1=0.56; KF=0.0; values of VMAX1 and KM1 in Table S-3 and 'Posterior Parameters' spreadsheet are 0.0035 and 0.55, respectively. Changing VMAX1 and KM1 to 0.0035 and 0.55 had minimal impact on plots. PROT = 1.0; use of PROT = 2.0 changes simulation results in plot slightly but noticeably.	VMAX1 and KM1 set to 0.0035 & 0.55, PROT = 2.0.
FRatKidneyMCMC1lvl.m	VVIAL, VINJ, and other system parameters set at top of script match **except** PROT = 2.0; numerical assignments on lines 98-99 match.	
Male_rat_liver.m	VINJ=0.0003858; VVIAL=0.0119573; VMAX1=0.071; KM1=0.35; KF=0.0;	
MRatLiverMCMCrun.m	VVIALM, VINJM, and other system parameters set at top of script match; numerical assignments on lines 100-105 also match.	
Male_rat_lung.m	VINJ=0.0003858; VVIAL=0.0119573; VMAX1=0.0; KF=0.00087;	
MRatLungMCMCrun.m	VVIALM, VINJM, and other system parameters set at top of script match; numerical assignments on lines 93-98 also match.	
Male_rat_kidney.m	VINJ=0.0002; VVIAL= 0.01163; VMAX1 =0.0041; KM1=0.84; KF=0.0; PROT=1.0; use of PROT = 2.0 changes simulation results in plot slightly but noticeably.	PROT set to 2.0.
MRatKidneyMCMC1lvl.m	VVIAL, VINJ, and other system parameters set at top of script match, **except** PROT=2.0; numerical assignments on lines 89-90 match.	
mixed_human_liver.m	VINJ=0.0003858; VVIAL=0.0119573; VMAX1=0.052; KM1=0.32; KF=0.0; if human tissue sampling used VINJ=0.0004 L, this value should be used in script; testing the change had a very slight impact on the simulations as shown in the plot.	
HumanLiverMCMCrun.m	VINJ=0.0004 on line 22; VVIAL and other system parameters match;	??
mixed_human_lung.m	VINJ=0.0004; VVIAL=0.0119573; VMAX1=0.0; KM1=1.0; KF=2.73e-14;	
HumanLungMCMCrun.m	VVIAL, VINJ, and other system parameters set at top of script match; numerical assignments on lines 90-91 match.	